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| 10/527,055 | 05/18/2005 | Alfred Nordheim | 26653U | 7002 |

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Alexandria, VA 22314

| EXAMINER | |
|---|---|
| STEELE, AMBER D | |
| ART UNIT | PAPER NUMBER |
| 1639 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/527,055 | NORDHEIM ET AL. | |
| | Examiner | Art Unit | |
| | AMBER D. STEELE | 1639 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 April 2008 and 16 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3 and 5-22* is/are pending in the application.

4a) Of the above claim(s) *5,13 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6-12, and 14-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 March 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/18/05; 3/9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

## DETAILED ACTION

1. Please note: the examiner of record has changed. However, the Technology Center (TC1600) and Art Unit (AU1639) remain the same.

### *Status of the Claims*

2. Claims 1-24 were originally filed on March 9, 2005.

The preliminary amendment to the clams received on March 9, 2005 amended claims 1-22 and canceled claims 23-24.

The amendment to the claims received on January 16, 2009 canceled claim 4.

Claims 1-3 and 5-22 are currently pending.

Claims 1-3, 6-12, and 14-21 are currently under consideration.

### *Election/Restrictions*

3. Applicant's election with traverse of Group I (claims 1-3 and 5-21) in the reply filed on April 14, 2008 is acknowledged. The traversal is on the ground(s) that a serious search burden does not exist. This is not found persuasive because the present application is a National Stage (371), therefore, the restriction is based on Lack of Unity. Since applicants have failed to traverse the Lack of Unity based on the either the common technical feature or the art utilized to break the unity of invention, applicants arguments are not persuasive. See MPEP § 823 and § 1893.03(d).

The requirement is still deemed proper and is therefore made FINAL.

4. Claim 22 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on April 14, 2008.

5. Applicant's election with traverse of proteins as the species of molecule and silver nitrate as the metal compound in the reply filed on January 16, 2009 is acknowledged. The traversal is on the ground(s) that the species requirement for a species of molecule is improper because all of the molecules (i.e. proteins, peptides, and nucleic acids) can all be detected by generic silver staining (applicants cite MPEP § 1850 III A) and that any silver compound is suitable as long as it is able to provide silver ions. This is not found persuasive because MPEP § 1850, section III, subsection A refers to the practice of potentially examining multiple inventions (e.g. product and process inventions examined together, product and apparatus inventions examined together, etc.) and does not support applicants assertion that the species requirement for a species of molecule is improper because all of the molecules (i.e. proteins, peptides, and nucleic acids) can all be detected by generic silver staining. In addition, it is noted that applicants have actually not elected a single, specific species of molecule, but rather a subgenus (i.e. proteins). However, the species election is accepted at this time. If claims to single, specific species are added later, a further species requirement may be required. Regarding applicants' comments about proteins and peptides, while the basic building blocks of proteins and peptides are the same (i.e. amino acids), proteins have additional secondary and tertiary folding structures that differ from short peptides. Therefore, peptides and proteins are structurally different. Applicants arguments regarding the species of metal, appear to be based on electing a specific metal compound (e.g. silver nitrate) as

opposed to a specific metal. Applicants are invited to clearly state on the record that every silver compound is an obvious variant. Such an admission on the record would require only a specific metal (e.g. silver) to be elected.

The requirement is still deemed proper and is therefore made FINAL.

6. Claim 13 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 16, 2009.

7. Applicant's election of X-R wherein X is a reducing moiety (i.e. vitamin) and R is the hydrophobic moiety (i.e. acyloxy radical) as the bifunctional agent, polyacrylamide as the species of solid support, ethanol as the species of alcoholic solution, EDTA as the species of complexing agent, and sodium thiosulfate as the species of developing solution in the reply filed on January 16, 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). It is noted that applicants have neglected to elect a single, specific species of bifunctional agent, but rather elected a subgenus (i.e. vitamin-acyloxy radical). The election is accepted at the present time, however, if claims are added to single, specific species of bifunctional agent, a supplemental species election may be required.

8. Claim 5 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on January 16, 2009.

***Priority***

9. The present application claims status as a National Stage (371) of PCT/EP03/09923 filed on September 8, 2003 and claims foreign priority to German application 102 43 303.8 filed September 13, 2002.

10. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. Please note: a translation was not submitted.

***Information Disclosure Statement***

11. The information disclosure statement (IDS) submitted on May 18, 2005 is being considered by the examiner.

12. The information disclosure statement (IDS) submitted on March 9, 2005 is being considered by the examiner in part (see below).

13. The information disclosure statement filed March 9, 2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. Copies of the NPL references were not provided.

***Sequence Compliance***

14. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Figures 4A, 4B, and 4C contain sequences without proper SEQ ID NOs:.

Applicant is requested to return a copy of the attached Notice to Comply with the reply.

***Drawings***

15. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: Figure 2 is not described and while Figure 4 is describe in general, Figures 4A, 4B, and 4C are not described. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or **amendment to the specification to add the reference character(s) in the description** in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

***Invention as Claimed***

16. A method for detecting molecules, in particular peptides, proteins, carbohydrates, glycoproteins, proteoglycans, and nucleic acids, by means of a metal compound in the presence of at least one bifunctional agent, said agent having at least one hydrophobic moiety and at least one reducing moiety and variations thereof.

***Claim Objections***

17. Claim 1 is objected to because of the following informalities: "at least one at least bifunctional agent" should read "at least one bifunctional agent". Appropriate correction is required.

18. Claim 6 is objected to because of the following informalities: the claim contains improper Markush language (i.e. from the group consisting of vitamin A, vitamin C, **or** vitamin E; see MPEP § 2173.05(h); from the group consisting of..., **and**...). Appropriate correction is required.

19. Claim 10 is objected to because of the following informalities: deletion of "=" is suggested for consistency within the claim. Appropriate correction is required.

20. Claim 16 is objected to because of the following informalities: clarification of "metal compound step" is requested (e.g. addition of metal compound, etc.). Appropriate correction is required.

21. Claim 6 is objected to because of the following informalities: the recitation of both vitamin C and ascorbic acid is redundant. Appropriate correction is required.

22. Claim 8 is objected to because of the following informalities: "at least" should be "at least one", etc. Appropriate correction is required.

***Claim Rejections – 35 USC § 112***

23. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

24. Claims 1-3, 6-12, and 14-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. One of skill in the art would not be able to determine the scope of the presently claimed invention. For example, the preamble reads "[a] method for detecting molecules" however the claim does not recite any method steps (e.g. providing a metal compound in the presence of at least one bifunctional agent). In addition, a nexus between the preamble and body of the claim is not present. In addition, the claim utilizes "by means of" language. Therefore, it is not clear if applicant is attempting to write the claim in "means for" language (see MPEP § 2181), if the claim language is open, or if the claim language is closed.

25. Regarding claim 6, the phrase "for example" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d). In addition, it is unclear if the claim requires only a vitamin (i.e. genus);

one of the Markush members of vitamin A, vitamin C, or vitamin E; or the species of ascorbic acid (i.e. vitamin C).

26. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear if the claim requires the "supergenus" of molecules or the "genuses" of peptides, proteins, carbohydrates, glycoproteins, proteoglycans, or nucleic acids.

27. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear if the claim requires the genuses of saturated hydrocarbon or monounsaturated hydrocarbon or the subgenuses of acyloxy radical, amyl radical, or alkyl radical.

28. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear if the claim requires n to be a range from 8-21, a range from 11-17, or 15.

29. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. It is not clear if the claim requires a final concentration from $10^{-5}$ to 1%, from $10^{-4}$ to 0.1%, $5x10^{-4}$ to $5x10^{-3}$, or $10^{-3}$%.

30. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear if the claim requires the subgenus of silver compound or the species of silver nitrate.

31. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear if the claim requires the subgenuses of gel, membrane, or microarray support or the species of a polyacrylamide gel, an agarose gel, a PVDF membrane, a mitrocellulose membrane, or a biochip.

32. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear if the claim requires the molecules to be on or in a support or not.

33. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear if the claim requires the bifunctional agent to be in a fixing solution or not.

34. Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear if the claim requires the bifunctional agent to be in a fixing solution or not and if the alcoholic solution is ethanol or not.

35. Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear if the claim requires the genus of complexing agent or the species of EDTA or EGTA and if the complexing agent is present in a developing solution or not.

36. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear if the claim requires the genus of reducing agent or the species of formaldehyde, sodium carbonate, or sodium thiosulfate. In addition, it is not clear if the developing solution comprises a reducing agent, a complexing agent, or a combination of both.

37. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear if the claim requires the genus of characterized or the species of mass spectrometrically.

38. Claim 3 recites the limitation "X" in line 1. There is insufficient antecedent basis for this limitation in the claim. Dependency on claim 2 is suggested.

39. Claim 18 recites the limitation "the fixing solution" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim. Dependency on claim 17 is suggested.

40. Claim 19 recites the limitation "the developing step" in line 2. There is insufficient antecedent basis for this limitation in the claim.

***Claim Rejections - 35 USC § 103***

41. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

42. Claims 1-3, 6-12, and 14-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Merril U.S. Patent 4,405,720 issued September 20, 1983; Tsuzuki et al. U.S. Patent 5,922,529 issued July 13, 1999; Diwu et al. U.S. Patent 6,329,205 issued December 11, 2001; and Rabilloud, 1990, Mechanisms of protein silver staining in polyacryalmide gels: a 10-year sysnthesis, Electrophoresis, 11: 785-794 (provided by applicants in the IDS).

For present claims 1, 12, 14-16, and 18, Merril teaches methods of silver staining polypeptides in polyacrylamide gels comprising fixing with ethanol, washing, adding silver nitrate, developing including utilizing various developers (i.e. reducing agents), stopping, and

analysis (please refer to the entire specification particularly the abstract, columns 1-8; Examples 1, 3, 6; claims).

However, Merril does not teach a reducing agent of ascorbyl palmitate or ascorbyl stearate.

For present claims 1-3, 6-12, 14-18, and 20, Tsuzuki et al. teach methods of silver staining utilizing polyacrylamide gels comprising utilizing ascorbyl palmitate or ascorbyl stearate as reducing agents to reduce silver ions into metallic silver at concentrations of 0.05 to 0.5 mol per mol of silver, utilizing ethanol, silver nitrate, and sodium thiosulfate (please refer to the entire specification particularly the abstract; columns 1-4, 50, 54-55, 57, 59; Example 1).

However, neither Merril nor Tsuzuki et al. teach mass spectrometry.

For present claim 21, Diwu et al. teach methods of staining proteins in polyacrylamide gels wherein silver staining is added as a secondary stain and analyzing the proteins by mass spectrometry (please refer to the entire specification particularly the abstract; columns 1-2, 17, 19, 21-23).

However, Nerril, Tsuzuki et al., and Diwu et al. do not teach EDTA.

For present claim 19, Rabilloud teaches methods of silver staining proteins in polyacrylamide gels comprising fixing, washing, addition of silver nitrate, developing, and stopping wherein alternative developers and other reagents are discussed including ethanol, EDTA, and sodium thiosulfate (i.e. Farmer's reducer; please refer to the entire reference particularly sections 1, 2.1, 2.2, 2.3, 2.4.3, 3.3.1, 4; Table 1).

The claims would have been obvious because the substitution of one known element (i.e. various developers/reducing agents taught by Merril) for another (i.e. ascorbyl palmitate or

ascorbyl stearate taught by Tsuzuki et al.) would have yielded predictable results (i.e. reduce silver ions into metallic silver) to one of ordinary skill in the art at the time of the invention. In addition, the claims would have been obvious because a particular known technique (i.e. mass spectrometry taught by Diwu et al.) was recognized as part of the ordinary capabilities on one skilled in the art. Furthermore, the claims would have been obvious because the substitution of one known element (i.e. various reagents taught by Merril) for another (i.e. EDTA taught by Rabilloud) would have yielded predictable results (i.e. chelating metal ions, reducing background via binding free silver ions) to one of ordinary skill in the art at the time of the invention. See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

***Future Communications***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMBER D. STEELE whose telephone number is (571)272-5538. The examiner can normally be reached on Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Amber D. Steele/
Patent Examiner, Art Unit 1639

March 5, 2009